UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

February 19, 2016

MEMORANDUM:

Subject:	Name of Pesticide Product:	T2.200 FOR DOGS
	EPA Reg. No. /File Symbol:	91384-G
	DP Barcode:	DP 431032
	Decision No.:	511951
	Action Code:	R315
	Submission:	#978275
	PC Codes:	109701 (Permethrin: 44.00%) 129099 (Imidacloprid: 8.80%) 129032 (Pyriproxyfen: 0.44%)
From:	Byron T. Backus, Ph.D., Toxicologist CITAB Registration Division (7505P)	Byron T. Backus Feb-19-2016
Through:	Masih Hashim, Ph.D., Team Leader, Toxicology CITAB Registration Division (7505P)	MHashim
To:	Elizabeth Fertich IVB1 Registration Division (7505P)	
Registrant:	CAP IM SUPPLY, INC.	

FORMULATION FROM LABEL:

Active Ingredients:	by wt.
129099 Imidacloprid	8.80%
109701 Permethrin	44.00%
129032 Pyriproxyfen	0.44%
Other Ingredients:	46.76%
TOTAL	100.00%

ACTION REQUESTED: "Please complete a 90-day screen by 3/14/16… Review the submitted companion animal toxicity data and prepare a memo. The following items are attached:

1. cover letter; 2. label; 3. hard copies of studies; 4. data matrix…"

BACKGROUND:

The material received includes a cover letter dated December 3, 2015; a data matrix (dated December 23, 2015) citing two (puppy and adult dog) companion animal safety studies; and a proposed label (proposed dosage rates: 0.4 mL for dogs and puppies weighing 4-10 lbs; 1.0 mL for 11-20 lbs; 2.5 mL for 21-55 lbs; and 4.0 mL for >55 lbs.

COMMENTS AND RECOMMENDATIONS:

1. Significant reporting deficiencies (see below) have been identified in a screening review of the companion animal safety study in beagle puppies (MRID 49788722). These deficiencies have to be adequately addressed before the study can be fully reviewed.

   According to information on page 30 of MRID 49788722, there was a single occurrence of "slight inappetance" (in Group 4 animal 5A2 CBA on Day 1) following administration of the test (or control) substance. "Slight inappetance" is not defined (which is, in itself, a reporting deficiency), although from page 1414 of MRID 49788722 this animal consumed 0-25% (as measured on Day 1) of the food that was offered on Day 0. In a previous report (Study No. 4464) from this laboratory inappetance was defined as consumption of < 25 g dry food/day.

   However (from p. 1414 of MRID 49788722), the same puppy (5A2 CBA) consumed only 0-25% (as measured on Day 11) of the food that was offered on Day 10; from p. 1419 of MRID 49788722 Group 4 puppy 5A4 2FD consumed 0-25% of the food offered on Day 11, from p. 1424 Group 4 puppy 5A7 D8F consumed 0-25% of the food offered on Days 9 and 18, from p. 1426 Group 4 puppy 5A7 E00 (described on p. 30 as listless and with diarrhea on Day 1, but not as showing inappetance) consumed 0-25% of the food offered on Days 0 and 6, from p. 1430 Group 4 puppy 5A8 8F3 consumed 0-25% of the food offered on Day 40. For the control (Group 1) puppies 5A4 191 consumed 0-25% of the food offered on Days 5 and 9 (p. 1384), 5A6 6BA consumed 0-25% on Day 0 (p. 1389), 5A6 AAC consumed 0-25% on Day 13 (p. 1392), 697 FFA consumed 0-25% on Days 0 and 1 (p. 1402) and 0-25% on Day 36 (p. 1403), and 698 0C0 consumed 0-25% on Day 1 (p. 1404). It is concluded that these represent occurrences of inappetance which the summary on page 30 does not report; the summaries should either be corrected or an explanation should be given as to why these incidents should not be a part of these summaries.

An additional concern is that there may be a similar reporting problem with clinical signs. For this reason, all individual twice daily observations (not just occurrences or summarizations of possible adverse effects) should be submitted to the Agency.

From page 23 of MRID 49788722: "The Test/Control Substance was applied topically, divided in two to four spots on the dorsal midline from the shoulders to the base of the tail. All pups weighed less than 9.5 kg and received two spots. Multiple doses were applied in divided doses over a period of no more than two hours to the pups in groups 1 and 4." No information is provided as to how cumulative 5X doses were applied (such as two 2½X doses, or five 1X doses), how much time there was between doses, or whether the application site was allowed to dry between doses. This information should be provided. The report should also state whether the test material to the same site or just the same general area when it was applied multiple times during the space of 2 hours. In addition, draft labeling (submitted December 3, 2015) states (p. 11) that for dogs weighing 4-10 lbs and 11-20 lbs: "Apply the entire contents of the applicator to one spot as shown." This spot would be on the dog's back between the shoulder blades, so there is an inconsistency between the way the test/control materials were applied (to 2 spots) in this study and the directions for use. This inconsistency has to be addressed.

On Day -1 all puppies weighed less than 5 kg so (from dosage rates given on p. 22) it is assumed they all received 2.0 mL (5 x 0.4 mL) of either test or control substance. However, from information on pages 1376 and 1377 one control (male 698 4D1) and two Group 4 (male 5A3 1B0 and female 5C3 CC8) weighed slightly more than 5.0 kg on Day 29 and should have each received cumulative doses of 5.0 mL of test/control material on Day 30, which should be confirmed. In addition, it is stated (p. 25) that: "Body weights were recorded to two or three decimal points but were rounded up to one decimal point for purposes of dose calculation..." From p. 1377 two Group 4 puppies, female 57B 202 and female 5D1 0EA, weighed 4.91 and 4.94 kg, respectively, on Day 29. The report should state whether these puppies received cumulative doses of 2.0 or 5.0 mL test material on Day 30.

2. A number of deficiencies have been identified in the companion animal safety study in adult beagles (MRID 49788721). These have to be adequately addressed before the study can be fully reviewed.

   Insufficient information was provided regarding administration of the test (or control) substance. From p. 21 of MRID 49788721: "Multiple doses were applied in divided doses over a period of no more than two hours to the dogs in Groups 3 and 4." Additional details should be provided as to how cumulative 3X and 5X doses were applied (such as two 1½X doses for the cumulative 3X, or two 2½X doses for the cumulative 5X), how much time there was between doses, and whether the application site was allowed to dry between doses. The report should also state whether the test material was applied to the same site or just the same general area when it was applied multiple times during the space of 2 hours.

In many cases, the report does not specify the individual dogs which showed signs. On page 33 it is noted that very slight erythema was present in Group 2 dog 5B3 E6F at 1 hour on Day 30, one unidentified dog in Group 3 had very slight erythema on Day 0 at 3 and 4 hours post-administration and on Day 1 at the first observation for the day, and six unidentified Group 4 dogs had very slight erythema on Day 30 at one hour post-administration, and one dog still had slight erythema at 2 and 3 hours post-administration. The report should identify (by animal ID) the dogs that were affected.

The report gives a brief summary (Table H, page 33) of specific post-administration observations. There is no mention of "inappetance." An examination of the individual food consumption data shows (p. 1857) that Group 2 dog DF5 B71 consumed 0-25% of the food offered on Day 0, and (from p. 1888) Group 3 dog CBC 683 consumed 0-25% of the food that was offered on Days 2, 3, 4 and 12, but there is nothing in Table H about these occurrences. As with the puppy study, <u>all</u> individual twice daily observations (not just summarizations of possible adverse effects) should be submitted to the Agency.